PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Body mass index variation over time and associated factors among HIV positive adults on second-line ART in Northwest Ethiopia: A retrospective follow up study
AUTHORS	Baraki, Adhanom; Gezie, Lemma Derseh; Zeleke, Ejigu; Awoke, Tadesse; Tsegaye, Adino Tesfahun

VERSION 1 – REVIEW

REVIEWER	Mar Pujades-Rodriguez University of Leeds, UK
REVIEW RETURNED	16-Apr-2019

GENERAL COMMENTS	Manuscript ID bmjopen-2019-030550 now in your Reviewer Center - BMJ Open Reviewer Comments: Barki et al. conducted a hospital-based cohort study among adult patients treated with second line ART therapy. The authors extracted data from the registration cards of the patients and studied changes in BMI over a median time of 18 months. They also investigated factors associated with changes in BMI. I read the manuscript with great interest. However, I have concerns about the methodological approach adopted in this research. I summarise these and other comments below. Abstract Objective: please replace 'the trend of body mass index' by the 'change in' or 'evolution of' Design: it is probably best to clearly mention here (instead of in the 'Participants' paragraph) that the study was conducted using data extracted from patient cards and the period of extraction. Participants: You probably need to mention here that these were HIV patients starting second line therapy. Outcome: shouldn't this be the change in BMI since baseline (clearly stating what baseline means). Results: It might be best to spell out what the beta coefficient means so it is clear for readers without statistical/epidemiological training. Strengths and limitations: Line 46: please clarify the second bullet point. Lines 47-49: Could you clarify the second sentence? A longitudinal analysis by itself does not ensure that estimations derived from data with missing values and measured at different time points are valid.

	Lines 50-51: please specify that these are BMI measurements and also the median number and IQR per patient as well as the median time between measurements. Could you also clarify how many patients had baseline BMI? Background Lines 70-71: It is not BMI but a 'low BMI' what is used in the criteria for the clinical definition of AIDS. Line 74: I could not find the 'BMI <=18.5 kg/m2' amongst the criteria for the clinical definition of stage 2. Line 83: Could you clarify what the gap in the literature is? Lines 84-85: You need to specify that you are referring to the evolution of BMI following the start of second line treatment. Lines 85-87: Please clarify the last two sentences. Methods and material Lines 90-91: Please clarify the definition of 'adult' and also what is meant by 'enrolled'. E.g. Were these patients eligible if they started second line therapy during the study period? Study area and population: please clarify how many referral hospitals were included (number and proportion of those in the region). Could you also clarify whether second line therapy is only provided in referral hospitals or not (e.g. how representative are the patients included?) and provide information on the definition of second line therapy and how patients on second line therapy are managed and monitored. Sample size and sampling procedures: Please provide also the percentage of those included. Line 100: please replace 'were used for multivariable analysis' by 'were included in the study'. Could you also clarify whether all the patients had a baseline BMI measure (and how baseline was defined). Data collection procedures: were HIV patient registration cards hold in the hospital or by the patients (this has implications on the likelihood that some potentially eligible patients were or not excluded). Please also add 'results of laboratory tests' (e.g. CD4 cell count). Please explain how adherence was measured and how baseline was defined (was this the start of second line therapy?). Data structure, compilation and analysis strategy: Line 107: Please clarify what you mean by 'data was cleansed' Please clarify the definition of your outcome (is this BMI or change in BMI in relation to baseline?), the start and end of follow-up, your definition of lost to follow-up, how deaths, lost to follow-up and missing data on risk factors/covariates were handled. This is extremely important to assess the validity of the estimations. Please clarify what risk factors were considered and your strategy (some factors might be highly correlated or in the pathway between the exposure and the outcome) for adjustment and when these were measured (if at baseline, please clarify what baseline is). Did you have information on the regimen provided for first line treatment and its duration? Did all patients started on second line receive the same ART regimen? Did you have information on toxicities? Lines 114-117: Please clarify how the linear mixed effect model was specified. Did you take into account the hospital were the

	treatment was provided? How the model was selected? How linearity of BMI was assessed? Changes in BMI are likely to be more rapid during the first months of treatment. As the median of follow-up was 18 months, it is unlikely that the change in BMI was linear during this long period. Results Line 131: Do you mean 'adult patients started on second line ART' as opposed 'to being already receiving second line ART'? Lines 135-136: Please clarify that you are referring to measurements of weight per patient. Please provide information about the time between measurements (median and IQR). In supplementary material, it would be useful to provide the number of patients according to the number of measurements and the median time between measurements for each group. This is important to appraise the validity of the results. Line 137: Table 1 does not include information on the BMI measurements. Exploratory analyses: I suggest to include these as part of Supplementary material although relevant information (e.g. use of AIC) should be included in the methods and descriptive information on BMI should appear in the main paper (median, IQR and proportions of patients with BMI <18.5 and >=30). You might also want to provide a locally weighted smoothed spline (LOWESS) curve. It would also be useful to provide information on yearly average BMI increase since the start of second line therapy. Line 171: Please clarify whether time since treatment refers to first or second line therapy. Discussion Lines 206-209: Please clarify. Line 216: Being bedridden is likely to be related to having an opportunistic infection, which can also lead to weight loss. Tables 1 and 2 Please provide numbers of patients with missing data for each variable and include baseline BMI as well (ideally it would be useful to see this and the CD4 cell count at both the start of first line and the start of second line). Table 3 and 4 I suggest to move Table 3 to Supplementary material and provide the information in Table 4 as a footnote of Table 5. Figure 2 I suggest to change this and show only the LOWESS curve, maybe according to the baseline level of BMI. It is very difficult to read and interpret it as it is. MINOR COMMENTS There is a need for editorial editing of the article. It would be helpful for the reader if the IQR as presented in the paper by the values of P25 and P75. This gives a quicker idea of how the values of a particular variable were spread in the data.

	Please use Arabic numbers for the WHO clinical stage (stage 2 instead of stage II). Line 69: Please provide an updated reference about the number of people currently treated. Results: You might prefer to combine the 2 first sections (and combine Tables 1 and 2 into one). Tables: You need to provide footnotes with the abbreviations.

REVIEWER	N Martinson Perinatal HIV Research Unit
REVIEW RETURNED	09-May-2019

GENERAL COMMENTS	This is a very interesting study and one which is timely. However, it is flawed by 1.Absence of the rationale for including individuals on second line ART and not including those on first line. 2. Unreported variables such as TB or other opportunistic or comorbid conditions, mortality, serial viral load and CD4 counts; all of which make it difficult to assess possible confounders 3. There is no mention of an IRB approval or waiver having been obtained. Finally ,the manuscript could do with a review by a first language English speaker with a science background. Also the instead of coefficients, the authors may want to consider hazard ratios or odds ratios to report risks. The figures of BMI with time are not that helpful. It looks like there are several patterns of weight change, those that go up , stay the same or decrease over time. Could this not replace the graphs.

VERSION 1 – AUTHOR RESPONSE

Reviewer #1 (Dr. Mar Pujades-Rodriguez) Comment #1: In the abstract section

Objective: please replace 'the trend of body mass index' by the 'change in' or 'evolution of'
Design: it is probably best to clearly mention here (instead of in the 'Participants' paragraph) that the study was conducted using data extracted from patient cards and the period of extraction.
Participants: You probably need to mention here that these were HIV patients starting second line therapy.
Outcome: shouldn't this be the change in BMI since baseline (clearly stating what baseline means).
Results: It might be best to spell out what the beta coefficient means so it is clear for readers without statistical/epidemiological training.

Authors' response #1: Dear Dr. Mar Pujades-Rodriguez thank you for your constructive comments and suggestions. We have corrected the objective by re stating it as "This study aimed to assess the evolution of Body Mass Index of HIV positive adults on second line ART over time and factors affecting it in Northwest Ethiopia" (Abstract section, Page 2 line 20-21)
Dear Dr. Mar Pujades-Rodriguez, we have found the comment on the Design appropriate and have edited it as "Institution based retrospective follow up study was conducted using data extracted from 1016 patient cards from February 2008 to February 2016." (Abstract section, Page 2 line 22-23)
We have revised the Participants in the abstract section as "HIV patients starting second line antiretroviral therapy" (Abstract section, Page 2 line 25)

Outcome was also corrected as “Change in BMI since starting second line antiretroviral therapy” (Abstract section, Page 2 line 26)
To make the results more understandable by all readers we have included a statement stating “The amount of BMI increment or decrement according to each variable was shown as β coefficient,” in the result section of the abstract (Page 2, lines 29-30)

Reviewer #1 (Dr. Mar Pujades-Rodriguez) Comment #2: Strengths and limitations:
Line 46: please clarify the second bullet point.

Authors’ response #2: The second bullet was made clearer by restating it as “The study is not based only on patient cards that started the second line antiretroviral therapy at the same point in time and also the length of follow up period for each participant was not equal across all participants.”
Reviewer #1 (Dr. Mar Pujades-Rodriguez) Comment #3: Lines 47-49: Could you clarify the second sentence? A longitudinal analysis by itself does not ensure that estimations derived from data with missing values and measured at different time points are valid.

Authors’ Response #3: Dear Doctor, to the best of the authors knowledge and experience and also according to our study, longitudinal data analysis is the best approach for unstructured and unbalanced data than any other statistical approach.
Reviewer #1 (Dr. Mar Pujades-Rodriguez) Comment #4: Lines 50-51: please specify that these are BMI measurements and also the median number and IQR per patient as well as the median time between measurements. Could you also clarify how many patients had baseline BMI?

Authors’ response #4: Dear Dr. Mar Pujades-Rodriguez we have revised this section per your suggestions as “Besides we had a total of 3568 number of BMI measurements taken from 1016 participants with a median BMI of 20.57 Kg/m2 (IQR = 4.675 Kg/m2). Baseline BMI was calculated for all 1016 patients. These will again strength the precision of the estimates.”
The median time between each weight measurement was 6.7(P25=4.27, P75=10.03), 6.08(P25=4.14, P75=9), 6.13(P25=4.2, P75=8.9), 6.27(P25=4.53, P75=8.9), 5.9(P25=3.97, P75=7.79), 5.83(P25=3.7, P75=8.13), 5.45 (P25=3.37, P75=7.43), 4.86(P25=2.97, P75=6.2), 5.19(P25=3, P75=7.37), 5.97(P25=4.23, P75=7.04), 5.55(P25=2.83, P75=5.86) and 3(P25=0.9, P75=4.84) months from first to twelfth weight measurement respectively.

Reviewer #1 (Dr. Mar Pujades-Rodriguez) Comment #5: Background
Lines 70-71: It is not BMI but a ‘low BMI’ what is used in the criteria for the clinical definition of AIDS.

Authors’ response #5: Thank you Dr. we have corrected it by stating “Low BMI is recognised as one of the first criteria for the clinical definition of Acquired Immune Deficiency Syndrome (AIDS).”

Reviewer #1 (Dr. Mar Pujades-Rodriguez) Comment #6:
Line 74: I could not find the ‘BMI <=18.5 kg/m2’ amongst the criteria for the clinical definition of stage 2.

Authors’ response #6: Dear Dr. Mar Pujades-Rodriguez, I am afraid this is a misunderstanding the above mentioned criteria is for stage 3 and not stage 2.

Reviewer #1 (Dr. Mar Pujades-Rodriguez) Comment #7:
Line 83: Could you clarify what the gap in the literature is?

Authors' response #7:
Dear sir, the literature are limited is to mean that there is little information regarding the evolution of BMI over time and the factors affecting it. Even if there are few literatures they used either the end points (Two measurements, the beginning and the end). They fail to consider each measurement taken during the patients follow up period.

Reviewer #1 (Dr. Mar Pujades-Rodriguez) Comment #8:
Lines 84-85: You need to specify that you are referring to the evolution of BMI following the start of second line treatment.

Authors' response #8:
Dear Sir, we have corrected the statement according to your suggestion as "Even though BMI evolution is a very important and easily calculable tool that can predict treatment outcome, dropout from treatment, CD4 recovery and death literatures about its evolution across treatment time and factors affecting it are limited." (Background section Page 3-4 lines 84 - 86)

Reviewer #1 (Dr. Mar Pujades-Rodriguez) Comment #9:
Lines 85-87: Please clarify the last two sentences.

Authors' response #9: Dear sir, we have made them clearer by stating as
" Therefore this study tried to fill this information gap by determining the BMI evolution over treatment time and identifying the key factors affecting it. Information generated by this study will contribute to monitor the response of patients for antiretroviral therapy." (Background section Page 3 lines 86-89)

Reviewer #1 (Dr. Mar Pujades-Rodriguez) Comment #10: Methods and material
Lines 90-91: Please clarify the definition of 'adult' and also what is meant by 'enrolled'. E.g. Were these patients eligible if they started second line therapy during the study period?

Authors' response #10: Dear sir we have made improvements by restating it as "An institution based retrospective follow up study was conducted among adults, age 24 and above, who are taking second line ART from February 2008 to February 2016." We included those who have baseline height and at least two weight measurements within the study period pregnant women are also excluded from the study.

Reviewer #1 (Dr. Mar Pujades-Rodriguez) Comment #11:
Study area and population: please clarify how many referral hospitals were included (number and proportion of those in the region). Could you also clarify whether second line therapy is only provided in referral hospitals or not (e.g. how representative are the patients included?) and provide information on the definition of second line therapy and how patients on second line therapy are managed and monitored.

Authors' response #11: Thank you Doctor, we have revised it as "The study was conducted in Amhara regional state which is one of the nine administrative regions and two city councils of Ethiopia. The region constitutes majority of ART users in the country. The study population was adult HIV infected patients on second line ART in all the nine referral hospitals of the region. Second line ART is not provided only in referral hospitals but these institutions provide for more than 82% of patients on second line ART (We believe this represents the region). These institutions are also found across all the zones of the region.

The first-line treatment consists of a combination of two nucleoside/nucleotide reverse transcriptase inhibitors (NRTI) with one non-nucleoside reverse transcriptase inhibitor (NNRTI). Should failure of first-line treatment occur, a second-line treatment is implemented, using two NRTIs not previously used in first-line treatment, as well as one additional protease inhibitor (PI) (Methods section page 5 lines 95-102)

Reviewer #1 (Dr. Mar Pujades-Rodriguez) Comment #12:
Sample size and sampling procedures: Please provide also the percentage of those included.
Line 100: please replace 'were used for multivariable analysis' by 'were included in the study'. Could you also clarify whether all the patients had a baseline BMI measure (and how baseline was defined).

Authors' response #12: Thank you once again; there were a total of 1233 patients on second line ART in the study area and we have included all that fulfilled the inclusion and exclusion criteria (82.4% of the total). Dear sir from the included patient charts all had baseline BMI (Baseline BMI is the first weight in kg/ height in m2 measurement taken when the patient started second line ART). Line 100 is also replaced by ". . . were included in the study."

Reviewer #1 (Dr. Mar Pujades-Rodriguez) Comment #13:
Data collection procedures: were HIV patient registration cards hold in the hospital or by the patients (this has implications on the likelihood that some potentially eligible patients were or not excluded).
Please also add 'results of laboratory tests' (e.g. CD4 cell count).
Please explain how adherence was measured and how baseline was defined (was this the start of second line therapy?).

Authors' response #13:
The patient cards were kept in the hospital and no patient takes the patient cards home. Laboratory test result of CD4 cell count is reported as "The median CD4 count was 253 (P25=147, P75=399)» (Result section Page 7 Line 146).
Adherence to ART was assessed by pill counts at visits and is recorded as 'GOOD' (≥95% adherence) or FAIR (80%–95%), while POOR adherence is less than 80% (Methods Page 6 Lines 111-112) and any baseline measurement is taken at the start of second line therapy.

Reviewer #1 (Dr. Mar Pujades-Rodriguez) Comment #14:
Data structure, compilation and analysis strategy:
Line 107: Please clarify what you mean by 'data was cleansed' Please clarify the definition of your outcome (is this BMI or change in BMI in relation to baseline?), the start and end of follow-up, your definition of lost to follow-up, how deaths, lost to follow-up and missing data on risk factors/covariates were handled. This is extremely important to assess the validity of the estimations.

Authors' Response #14: Dear sir in this context data cleansing is to mean that the data was checked for inconsistencies and errors before data entry. The outcome variable in this study is the change in BMI over time. This is not just one measurement change as compared to the baseline instead several measurements (repeated measurements) as time goes on. A person who is absent for the next 3 months from the last appointment date was considered as lost to follow up. As you have suggested there was lost to follow up. But one of the most important strength of longitudinal data analysis is handling data that is measured in different time period among individuals and data that has missing values that could be due to missing or lost to follow ups, therefore using longitudinal data analysis ensures a valid estimate. Besides we had a total of 5380 number of measurements which is taken from 1016 participants. Therefore we believe the lost to follow up has a negligible effect on the estimates.

Reviewer #1 (Dr. Mar Pujades-Rodriguez) Comment #15:
Please clarify what risk factors were considered and your strategy (some factors might be highly correlated or in the pathway between the exposure and the outcome) for adjustment and when these were measured (if at baseline, please clarify what baseline is). Did you have information on the regimen provided for first line treatment and its duration? Did all patients started on second line receive the same ART regimen? Did you have information on toxicities?

Authors' Response #15:
Factors considered were Gender, Age, Educational Status, Occupational status, Adherence, Duration of Treatment, Isoniazide prophylaxis (INH), Cotrimoxazole Prophylaxis therapy (CPT), ART Regimen, WHO Stage, Tuberculosis, Opportunistic Infections, CD4 count, Functional status. Before fitting the model we have checked the presence of co-linearity by using variance inflation factor (VIF). Except for CD4 count, that was a time varying covariate all were taken once at the beginning of the second line regimen (Baseline). Since the focus of this study was on second line ART data about the first line regimens was not collected but the second line ART regimen was not the same for all patients and information about the drug toxicities was not collected.

Reviewer #1 (Dr. Mar Pujades-Rodriguez) Comment #16:
Lines 114-117: Please clarify how the linear mixed effect model was specified. Did you take into account the hospital were the treatment was provided? How the model was selected? How linearity of BMI was assessed? Changes in BMI are likely to be more rapid during the first months of treatment. As the median of follow-up was 18 months, it is unlikely that the change in BMI was linear during this long period.

Authors' Response #16:
Dear Dr. Mar Pujades-Rodriguez; the linear mixed effect model was selected because of the fact that the outcome variable was continuous variable with repeated measurements since repeated measurements from the same person are more likely to be correlated ignoring this correlation and fitting the standard linear regression will not be applicable.
Since all the hospitals included are referral hospitals and patients are treated with the same treatment guideline we did not assume any variation among hospitals.
The model was selected after comparison was made between (linear mixed effect model with only random intercept and the model with both random intercept and random slop) was made using likelihood ratio test. Different correlation structures were also compared using AIC and BIC values.
The linearity of BMI was assessed using the mean profile plot which shows a linear increment over time.
Dear sir as you have said the change in the BMI could be rapid during the first month of therapy but as you can see from the individual plot there is high variability in the change among patients both at the initiation and over time (Some with a high BMI with rapid deterioration and some with low BMI with a gradual increase). Since the increment is of the average, the variations are balanced over time and has resulted a linear increase.

Reviewer #1 (Dr. Mar Pujades-Rodriguez) Comment #17:
Results, Line 131: Do you mean 'adult patients started on second line ART' as opposed 'to being already receiving second line ART'?

Authors' response #17: Dear Sir, since this study is based on record review we have included those who are already on second line therapy and assessed the outcome status and other variables retrospectively. We have restated the sentence as "We had a total of 1016 adult patients who were taking second line ART" (Result section page 7 line 131)

Reviewer #1 (Dr. Mar Pujades-Rodriguez) Comment #18:
Lines 135-136: Please clarify that you are referring to measurements of weight per patient. Please provide information about the time between measurements (median and IQR). In supplementary material, it would be useful to provide the number of patients according to the number of measurements and the median time between measurements for each group. This is important to appraise the validity of the results.

Authors' response #18: Thank you it's corrected as "There were a maximum of 12 and a minimum of 2 measurements of weight per patient." (Result section page 7 line 135-136)
The time between measurements is included in the result section (Page 7 lines 137-142) as "The median time between each weight measurement was 6.7(P25=4.27, P75=10.03), 6.08(P25=4.14, P75=9), 6.13(P25=4.2, P75=8.9), 6.27(P25=4.53, P75=8.9), 5.9(P25=3.97, P75=7.79), 5.83(P25=3.7, P75=8.13), 5.45 (P25=3.37, P75=7.43), 4.86(P25=2.97, P75=6.2), 5.19(P25=3, P75=7.37), 5.97(P25=4.23, P75=7.04), 5.55(P25=2.83, P75=5.86) and 3(P25=0.9, P75=4.84) months from first to twelfth weight measurement respectively."

Reviewer #1 (Dr. Mar Pujades-Rodriguez) Comment #19:
Line 137: Table 1 does not include information on the BMI measurements.

Authors' response #19: Dear sir, its typing error the table is to refer the socio-demographic characteristics.
Reviewer #1 (Dr. Mar Pujades-Rodriguez) Comment #20:
Exploratory analyses: I suggest to include these as part of Supplementary material although relevant information (e.g. use of AIC) should be included in the methods and descriptive information on BMI should appear in the main paper (median, IQR and proportions of patients with BMI <18.5 and >=30). You might also want to provide a locally weighted smoothed spline (LOWESS) curve. It would also be useful to provide information on yearly average BMI increase since the start of second line therapy.

Authors' response #20:
Dear sir, we have included the exploratory analysis to show how variable the BMI of patients is from the baseline to their change over time. We believe this is an important information. The average BMI of patients is also presented in the updated manuscript (Result section page 7 lines 150-151).

Reviewer #1 (Dr. Mar Pujades-Rodriguez) Comment #21:
Line 171: Please clarify whether time since treatment refers to first or second line therapy.

Authors' response #21: Thank you we have corrected the comments on the exploratory analysis and we have corrected the second comment by mentioning it as "time since the start of second line ART"

Reviewer #1 (Dr. Mar Pujades-Rodriguez) Comment #22:
Discussion
Lines 206-209: Please clarify.
Line 216: Being bedridden is likely to be related to having an opportunistic infection, which can also lead to weight loss.

Authors' response #22: Dear sir, from line 206-209 we mean that when patients are taking ART drugs there will be suppression of the virus which halts the weight loss caused by it additionally the drugs also cause insulin resistance and weight gain.
In line 2016 we have used one of the commonest opportunistic infections (Diarrheal disease) which is known to cause weight loss as one of our justifications.

Reviewer #1 (Dr. Mar Pujades-Rodriguez) Comment #23:
Tables 1 and 2
Please provide numbers of patients with missing data for each variable and include baseline BMI as well (ideally it would be useful to see this and the CD4 cell count at both the start of first line and the start of second line).
Table 3 and 4
I suggest to move Table 3 to Supplementary material and provide the information in Table 4 as a footnote of Table 5.
Figure 2
I suggest to change this and show only the LOWESS curve, maybe according to the baseline level of BMI. It is very difficult to read and interpret it as it is.

Authors' response #23: Dear sir, we have added the missing number of patients in table-1 we believe the two tables (Table 3 and 4) are very important and including them will help for readers to be clear about the model therefore we have left them as they are and the LOWESS curve presented shows the trend over time which is the main objective of this study therefore reporting using only the baseline is not reasonable, with all due respect we have left this one as it is too.

Reviewer #1 (Dr. Mar Pujades-Rodriguez) Comment #24:
MINOR COMMENTS
There is a need for editorial editing of the article.
It would be helpful for the reader if the IQR as presented in the paper by the values of P25 and P75. This gives a quicker idea of how the values of a particular variable were spread in the data.
Please use Arabic numbers for the WHO clinical stage (stage 2 instead of stage II).
Line 69: Please provide an updated reference about the number of people currently treated.

Authors' response #19: Thank you we have accepted the comment and corrected and reported P25 and P75 for age, follow up time and CD4 counts. We have also replaced the Arabic number instead of Roman number while referring to WHO stages.

Reviewer #1 (Dr. Mar Pujades-Rodriguez) Comment #24:
Results:
You might prefer to combine the 2 first sections (and combine Tables 1 and 2 into one).
Tables:
You need to provide footnotes with the abbreviations.

Authors' response #24: Thank we Doctor, we have merged the two tables as you recommended and have added footnotes.

Reviewer: 2
Reviewer Name
N Martinson
Institution and Country
Perinatal HIV Research Unit
Please state any competing interests or state 'None declared':
None declared
Please leave your comments for the authors below

Reviewer #2 (Dr. N Martinson) Comment #1:
This is a very interesting study and one which is timely. However, it is flawed by 1.Absence of the rationale for including individuals on second line ART and not including those on first line.

Authors' response #1: Dear Dr. N Martinson, thank you for your constructive comments and suggestions. This study focused on patients on second line ART mainly because there are no more other options for physicians to choose from if second line therapy failed. And BMI of patients can easily be calculated and can also predict treatment outcome, dropout from treatment, CD4 recovery and death. Therefore close follow up and monitoring of response of patients on second line ART is vital.

Reviewer #2 (Dr. N Martinson) Comment #2:
2. Unreported variables such as TB or other opportunistic or comorbid conditions, mortality, serial viral load and CD4 counts; all of which make it difficult to assess possible confounders

Authors' response #2: Dear sir, we have considered all the above mentioned variables except the viral load, we have also mentioned this as a limitation of the study since it is based on secondary data. To control confounding factors we have used multivariable regression and also have selected the study participants randomly which makes the confounding factors distribute randomly.

Reviewer #2 (Dr. N Martinson) Comment #3:
3. There is no mention of an IRB approval or waiver having been obtained. Finally ,the manuscript could do with a review by a first language English speaker with a science background. Also the instead of coefficients, the authors may want to consider hazard ratios or odds ratios to report risks. The figures of BMI with time are not that helpful. It looks like there are several patterns of weight change, those that go up , stay the same or decrease over time. Could this not replace the graphs.

Authors' response #3: Thank you for these comments we have included IRB approval in the "Ethical consideration" section of the manuscript and since this is not a survival analysis we cannot interpret the findings as hazard rations nor as odds ratio. But we made the interpretation more understandable while the full manuscript is reviewed by a first language English speaker. And the several patterns of weight change is to show that each person has his or her own evolution even though their average change is increasing, and this shall be considered while considering a model for such changes.

VERSION 2 – REVIEW

REVIEWER	N Martinson Perinatal HIV Research Unit University of the Witwatersrand Johannesburg
REVIEW RETURNED	08-Aug-2019

GENERAL COMMENTS	Much improved manuscript Suggestions: 1. There should be more detail in the manuscript WHY you selected second line ART. Consider including some of the text you used in your response to my first review. 2. The repeated use of P25 and P75 is unusual. Suggest rather use define the interquartile range at its first use and then use (IQR: 123; 234). And maybe a box and whisker graph for those 12 BMIs over 18 months. 3. Line 158. Does the graph of 100 participants not suggest there may be errors in documenting weight at least in some patients where there are large steps over short time periods; suggest you include this in limitations? And for that graph could the month axis not be reduced from 100 months allowing a easier-on-the eye

	spread of the data; especially as the upper quartile of follow up is only 32 months? 4. Check spelling: slope not slop. Data cleaned not cleansed. 5. Is this correct terminology to use: "Keeping all the other variables constant..."? 6. line 201 include units for BMI increase. 7 line 230-232. What possible impact could the absence of these variables have on your inferences/analysis? 8. Provide citations for your use of linear effects model.

VERSION 2 – AUTHOR RESPONSE

Reviewer name: Dr. Neil Martinson

Comment#1: There should be more detail in the manuscript WHY you selected second line ART. Consider including some of the text you used in your response to my first review.

Authors' response #1: Dear Dr. Neil Martinson, we are grateful for your constructive comments and suggestions. We accept this comment and have mentioned the reason in the introduction section (page 5 lines 84-85) by stating it as "This study focused on patients on second-line ART mainly because there is no much option for physicians to choose from if second-line therapy failed."

Comment#2: The repeated use of P25 and P75 is unusual. Suggest rather use define the inter-quartile range at its first use and then use (IQR: 123; 234). And maybe a box and whisker graph for those 12 BMIs over 18 months.

Authors' response #1: Dear Dr. Neil Martinson, we have made corrections based on your suggestions for the IQR. We appreciate your suggestion on the box and whisker graph but with due respect, we did not include it in the updated manuscript for we believe it will be repetition of the same information. We have summarized the baseline BMI of patients in the result section (Page 9 lines 156-157) and also have presented the overall BMI (12 measurements) as a LOWESS smoothed curve (Figure-2).

Comment#3: Line 158. Does the graph of 100 participants not suggest there may be errors in documenting weight at least in some patients where there are large steps over short time periods; suggest you include this in limitations? And for that graph could the month axis not be reduced from 100 months allowing a easier-on-the eye spread of the data; especially as the upper quartile of follow up is only 32 months?

Authors' response#3: Dear Dr. Neil Martinson, Thank you once again. We share your concerns we have included the possible errors in documenting weight in the discussion section (Page 14 lines 244-245) as "The data may also have errors in documenting weight among some measurements."

Even though the upper quartile is 32.2 months we put the graph for the whole follow up period for we want to show what potential changes could be seen among the measurements beyond that. But we have made some improvements too (Reduced the time in months to 80).

Comment#4: Check spelling: slope not slop. Data cleaned not cleansed.

Authors' response#4: Thank you, Doctor, we have corrected the spelling errors and have tried to improve the full document in general.

Comment#5: Is this correct terminology to use: "Keeping all the other variables constant..."?

Authors' response#5: Dear Dr. Neil Martinson, Thank you for this nice question. It is a correct terminology, by saying this we can tell the association is not affected by the other variables (It is adjusted for these variables) therefore it is an independent predictor of the outcome status.

Comment#6: line 201 include units for BMI increase.

Authors' response#6: Thank you, Doctor, we have included it (Line 213).

Comment#7: line 230-232. What possible impact could the absence of these variables have on your inferences/analysis?

Authors' response#7: Dear Dr. Neil Martinson, Thank you. The absence of these variables has no effect on the data analysis but the inferences shall be seen in the light of these limitations because the possible effect of these variables is not determined.

Comment#8: Provide citations for your use of linear effects model.

Authors' response#8: Thank you, Doctor, we have cited in the method section (Page 6 line 124)